Investigating synapse formation and function using human pluripotent stem cell-derived neurons.

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Public Summary:
A major goal of stem-cell research is to identify conditions that reliably regulate their differentiation into specific cell types. This goal is particularly important for human stem cells if they are to be used for in vivo transplantation or as a platform for drug development. Here we describe the establishment of procedures to direct the differentiation of human embryonic stem cells and human induced pluripotent stem cells into forebrain neurons that are capable of forming synaptic connections. These findings establish human pluripotent stem cell-derived neurons as a viable model for the study of synaptic differentiation and function under normal and disorder-associated conditions.

Scientific Abstract:
A major goal of stem-cell research is to identify conditions that reliably regulate their differentiation into specific cell types. This goal is particularly important for human stem cells if they are to be used for in vivo transplantation or as a platform for drug development. Here we describe the establishment of procedures to direct the differentiation of human embryonic stem cells and human induced pluripotent stem cells into forebrain neurons that are capable of forming synaptic connections. In addition, HEK293T cells expressing Neuroligin (NLGN) 3 and NLGN4, but not those containing autism-associated mutations, are able to induce presynaptic differentiation in human induced pluripotent stem cell-derived neurons. We show that a mutant NLGN4 containing an in-frame deletion is unable to localize correctly to the cell surface when overexpressed and fails to enhance synapse formation in human induced pluripotent stem cell-derived neurons. These findings establish human pluripotent stem cell-derived neurons as a viable model for the study of synaptic differentiation and function under normal and disorder-associated conditions.

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